I. STRUCTURE OF CYCLIC VINYL TERTIARY AMINES

II. SYNTHESES OF HOMOLOGOUS TETRAHYDROCANNABINOLS

BY

KUANG HSU CHEN

B. S., National Tsing Hua University, 1933

M. S., University of Illinois, 1943

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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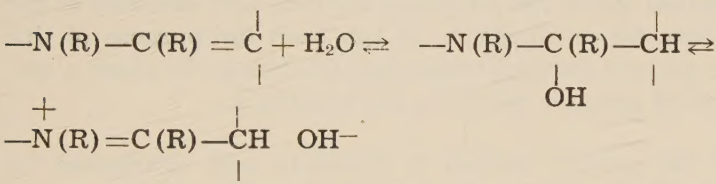
PART I

STRUCTURE OF CYCLIC VINYL TERTIARY AMINES

Basicity studies of vinyl tertiary amines have demonstrated that they are stronger bases than the corresponding saturated tertiary amines.[1] This pictures is the complete reverse of that presented by vinyl secondary amines, which are always weaker bases than the corresponding saturated secondary amines. Adams and Mahan have suggested an explanation of the enchanced basicity of vinyl tertiary amines in comparison with their saturated homologs. They have postulated that a vinyl tertiary amine, when brought into contact with water, becomes hydrated to a pseuda base which rearranges to a quaternary ammonium hydroxide. The quaternary ammonium hydroxides are known to be strong bases:



If the β-carbon atom in the original amine holds two different substituents, it will become asymetric in the quanternary base on account of the incoming hydrogen atom. Such amines should be resolvable in the form of two salts. The preparation and resolution of this kind of amines was undertaken in this research.

after several failures, 1,2-dimethyl-3-phenyl-Δ^2-tetrahydropyridine was obtained in a small amount. With *d*-tartaric acid, one solid bitartrate was obtained, an aqueous solution of which showed a specific rotation of $[\alpha]_D^{29.5}$—94.12°. The other expected salt could not be obtained in the solid form. It remained as a brown resin which was *dextro* rotatory. No sharp polarimeter reading could be determined on account of the yellow color of the solution.

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PART II

SYNTHESES OF HOMOLOGOUS TETRAHYDROCANNABINOLS

The search for the physiologically active principle in the resin prepared from hemp, *Cannabis sativa*, has been the constant effort of many chemists. Among the important discoveries achieved in this field is the method devised for synthesizing a tetrahydrocannabinol with the alicyclic double bond in conjugation with the benzene ring.[1] By applying this excellent method, numerous analogs and homologs have been synthesized and their activities studied. The maximum potency is found in the compound 1-hydroxy-3-*n*-hexyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran which has a potency value of 1.82 referring to the *n*-amyl homolog as standard. It has been the purpose of this thesis to prepare tetrahydrocannabinol homologs in which a secondary alkyl group is placed in the position 3.

With the general method of synthesis well established by Adams and Baker, the problem resolved itself into the preparation of the appropriate resorcinols. For this purpose 3,5-dimethoxyphenyl *n*-alkyl ketones were converted by treatment with appropriate Grignard reagents into carbinols which were subsequently dehydrated to olefins. Under the catalytic action of Raney nickel these olefins were hydrogenated at room temperature and under a pressure of two to three atmospheres, yielding 3,5-dimethoxyphenyl alkanes. Upon demethylation the desired resorcinols were obtained. Condensation with ethyl 5-methylcyclohexanone-2-carboxylate converted the resorcinols into dibenzopyrones which, with excess of methylmagnesium iodide, gave the desired compounds.

Five compounds were synthesized. These are: 1-hydroxy-3-(1-methylbutyl)-, 1-hydroxy-3-(1-ethylbutyl)-, 1-hydroxy-3-(1-methylpentyl)-, 1-hydroxy-3-(1-*n*-propylpentyl)-, and 1-hydroxy-3-(1-methylhexyl)-6,6,9-trimethyl-7,8,9,10-tetra-hydro-6-dibenzopyrans. All of the five compounds are more active than

the corresponding homologs in the *n*-alkyl series. The last compound exhibits a potency of 4.18, highest in the present series.

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VITA

The author was born in Kingtze Kwan, Honan Province, China, on December 1, 1905. He received his primary education in the Town School. In 1921, he entered Nan Kai Middle School, Tientsin, from which he graduated in 1926. After an interruption of two years, he enrolled in National Tsing Hua University, then at Peiping, in the fall of 1928, where he majored in chemistry. He graduated with the degree of Bachelor of Science in 1933.

After his graduation, he served as assistant in the Department of Chemistry at his Alma Mater. When he Japanese invaded China, he followed the University to Kunming. For his long service, the University granted him a partial scholarship to come to the United States in pursuit of advanced studies.

He entered the University of Illinois in February, 1942, and received the degree of Master of Science in 1943. Since then, he has been enrolled continuously in this institution. Since September, 1942, he held a tuition scholarship from the University.

The following are his more important publications:

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